Radiation Effects on the Thyroid: Emphasis on Iodine-131

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Introduction

The thyroid gland is a relatively large endocrine organ whose primary function is to regulate metabolism. It contains approximately 8-12 mg of iodine, i.e. about 90% of total body iodine. Cell division in the thyroid is frequent *in utero* and during early childhood, but is uncommon in the adult thyroid. These characteristics are important in terms of the tumorigenic effects of radiation exposure.

Although thyroid cancer is relatively rare – approximately 18,000 people develop it each year, i.e. 2% of cancers in women and <1% in men – incidence has been increasing in many parts of the world over the last several decades (Landis et al., 1999; Ron, 1996). Because large segments of the public have been exposed to environmental or medical radioiodines this increase has generated concern regarding their long-term health effects. Exposure to radioiodines, particularly iodine-131 (I-131) comes from atmospheric nuclear weapons tests, accidental releases from nuclear power plants, and emissions from nuclear weapons production facilities. Radioactive iodine also has been used frequently in nuclear medicine. Millions of adult patients underwent I-131 diagnostic exams before the introduction of iodine-123 and technetium pertechnetate (99mTc) scans and thyroid ultrasound (Becker, 1989). Currently, I-131 is the treatment of choice for thyrotoxicosis and is a common treatment for thyroid cancer (Becker and Hurley, 1996).

Some epidemiological and experimental data suggest that I-131 is not as effective in inducing thyroid malignancies as external radiation (NCRP, 1985; Shore, 1992; UNSCEAR, 1994). The biological effectiveness of I-131 is thought to be less than x - or gamma radiation because of differences in radiation quality and dose rate. However, the early and sharp increase in thyroid cancer incidence among children living near the Chernobyl accident

has become a catalyst for reevaluating the turmorigenic potential of I-31. The following summary of recent data on medical and environmental exposure to radiation emphasizes the differences between external radiation and I-131.

External Radiation

External radiation is the major known cause of thyroid cancer. At doses as low as 0.1 Gy, childhood exposure to x- or gamma radiation can sharply increase the risk. Among atomic bomb survivors, thyroid cancer has the third highest excess relative risk coefficient (Figure 1). For childhood exposure, it has the highest risk coefficient of all solid cancers.

Much of what is known about radiation-associated thyroid cancer comes from studies of the atomic bomb survivors (Thompson et al., 1995), as well as a pooled analysis of seven (5 cohort and 2 nested case-control) major epidemiologic studies of acute, external radiation (Ron et al., 1995). In the pooled analysis, almost 120,000 people (about 58,000 exposed and 61,000 non-exposed) with 3,000,000 person years of follow-up and 700 thyroid cancers were studied. The excess relative risks demonstrated a strong association between radiation and thyroid cancer in each of the studies of childhood exposure (less than age 15 years at the time of irradiation) for which a stable risk estimate could be obtained (Table 1). With the possible exception of the high-dose childhood cancer survivor study, the linear model fit the data well. Among the childhood cancer survivors there was some suggestion that a linear-exponential model might fit the data better than a linear model, however, the improvement in fit was not statistically significant. Combining the childhood exposure data, the excess relative risk (ERR) per Gy (ERR $_{1Gy}$) was 7.7 (95% confidence interval [CI] = 2.1-28.7) and the excess absolute risk per 10,000 person-year-Gy (ERR per 10^4 PYGy) was 4.4 (95% CI= 1.9-10.1). The ERR decreased with increasing age at exposure, so that among persons exposed as adults there was no evidence of a radiation effect. The largest risk was observed 15-19 years after exposure, but remained elevated 40 or more years after exposure. Women had a two-fold risk compared with men (p=0.07), however, this difference was not consistent across studies. Results from other investigations were consistent with the pooled analysis, e.g. in a Swedish cohort of infants and young children irradiated for skin hemangiomas, risk patterns were similar, but the risk estimates were somewhat smaller (ERR $_{1Gy}$ = 4.9; 95% CI = 1.3 - 10) (Lundell et al., 1994).

Table 1- *Thyroid cancer risk following childhood external radiation exposure*[a,b].

	ERR/Gy	95% CI
Individual Studies		
Enlarged thymus	9.1	(3.6, 28.8)
A-bomb survivors	4.7	(1.7, 10.9)
Tinea capitis	32.5	(14.0, 57.1)
Enlarged tonsils (MRH)	2.7	(0.6, 26.0)
Childhood cancer survivors[c]	1.1	(0.4, 29.4)
Pooled Study	7.7	(2.1, 28.7)

[a] Adapted from Ron, et al., 1995
[b] Childhood exposure refers to exposure at less than 15 years of age.
[c] ERR/Gy estimates based on setting doses under 2 Gy to the mean dose of 0.74 Gy.

Elevated risks of thyroid cancer have been reported often among children treated with high-dose radiotherapy for Hodgkin's disease, meduloblastoma, and other malignancies (Bhatia et al., 1996; Black et al., 1998; Goldstein et al., 1997; Hancock et al., 1991; Hawkins and Kingston, 1988; Sankila et al., 1996; Tucker et al., 1991). A dose-response has been observed in children receiving head and neck or whole body irradiation. Since the majority of pediatric cancer patients have a very good prognosis - the five-year relative survival rate for 1989-1994 was 74% for all childhood cancers and 92% for pediatric Hodgkin's disease (Landis et al., 1999) - people receiving radiation therapy for childhood malignancies should have routine thyroid examinations.

Protracted exposure, such as from multiple diagnostic x-rays or in an occupational setting, are of particular relevance to society because large numbers of the general population are affected. Although there have been some reports of elevated thyroid cancer risks associated with self-reported diagnostic x-ray procedures (Wingren et al., 1993; Hallquist et al., 1994), no relationship with frequency of examination or cumulative dose was found in a Swedish study which computer-linked radiology records of diagnostic x-rays to thyroid cancer cases and controls (Inskip et al., 1995). Results from recent evaluations of adult occupational exposure have been difficult to interpret. A few have been positive, but a dose-response relationship rarely has been demonstrated. Since the number of thyroid cancers in most of these studies was small, doses were low, exposure was during

adulthood, and mortality frequently was the outcome measure, occupational studies have not been particularly informative.

Medical Exposure to I-131

In contrast to the strong evidence of a dose-response relation between childhood exposure to external radiation and the development of thyroid neoplasia, relatively little is known about the carcinogenic effects of I-131 on the thyroid gland. Most studies have indicated that the medical use of I-131 in adults is not associated with large increases in thyroid cancer incidence, but the risk of developing thyroid cancer following childhood I-131 diagnostic or therapeutic exposure has not yet been quantified adequately.

The first major epidemiologic study of diagnostic I-131 was conducted by Holm and colleagues (1988; 1989). They linked a cohort of 35,000 Swedish patients examined with I-131 with the Swedish Cancer Registry to identify all malignancies and found no association between I-131 and the subsequent occurrence of thyroid cancer. Hall et al., (1996a) has updated the follow-up for the cohort through 1990. The mean age at first exam was 43 years and only 7% of the study population was under age 20 at the time of first exam. Less than 1% of the patients were under age 10. About 32% of the patients were referred for an I-131 examination because a thyroid tumor was suspected. The mean estimated dose to the thyroid gland was 0.8 Gy after adjusting for thyroid gland weight. Five or more years after exposure 67 thyroid cancers occurred, resulting in a standardized incidence ratio (SIR) of 1.4 (95% CI =1.1-1.7). Patients with a suspected thyroid tumor had an elevated risk (SIR=2.9; 95% CI=2.1-3.9), but no excess risk or dose response was seen for the patients referred for possible hypo- or hyperthyroidism or other reasons (SIR=0.8; 95% CI=0.5-1.1). Among slightly more than 2,000 patients examined with I-131 between the ages of 15 and 19 years, 3 thyroid cancers were observed (SIR=1.7; 95% CI=0.4-4.9); with 2 observed among the patients not referred for suspected thyroid tumors (SIR=1.4; 95% CI=0.2-5.0). The lack of a risk found for adult patients is similar to the finding for the atomic bomb survivors of the same age. The small, non-significant risk reported for the patients exposed to I-131 prior to age 20 is considerably lower, but probably not statistically incompatible, with the risk reported for the A-bomb survivors.

A total of 1,005 women exposed to diagnostic I-131 and a comparison group of 248 women of similar age undergoing a routine mammographic

screening exam participated in a clinical thyroid screening examination (Hall et al., 1996b). No thyroid cancers were detected and the prevalence of thyroid nodules was similar in the two groups examined, 10.6% and 11.7% in exposed and non-exposed, respectively (relative risk [RR]=0.9; 95% CI=0.6-1.4). The RR did not change when adjustment was made for potential confounders. Among the women examined with I-131, an association between benign thyroid nodules and estimated I-131 thyroid dose was observed (Table 2). The association was particularly strong for single nodules, and was not restricted to patients examined with I-131 because of suspicion of thyroid tumor or goiter. No age at exposure effect was noted, but only eight women had their I-131 examination before age 10 years.

Two major epidemiological studies of I-131 treatment for hyperthyroidism have been conducted. In Sweden, 10,522 hyperthyroid patients receiving therapeutic I-131 were evaluated for thyroid cancer incidence and mortality (Holm et al., 1991; Hall et al., 1992). A new follow-up of the Cooperative Thyrotoxicosis Therapy Follow-up Study (Dobyns et al., 1974; Saenger et al., 1968; Tompkins, 1970) recently was conducted in the U.S. (Ron et al., 1998). Cancer mortality was evaluated in approximately 23,000 patients

Table 2- *Thyroid nodule prevalence among Swedish women exposed to diagnostic I-131 examinations.*

Type of Nodule	Thyroid Dose (Gy)		
	≤ 0.25	0.25-1.00	> 1.00
Single			
No. women	26	19	23
RR (95% CI)	1.0	1.6 (0.8-2.9)	3.3 (1.7-6.3)
ERR/Gy (95% CI)		1.2 (0.4-3.2)	
Multiple			
No. women	14	16	9
RR (95% CI)	1.0	2.4 (1.1-5.1)	2.1 (0.8-5.2)
ERR/Gy (95% CI)		0.1 (0.4-1.5)	
Total			
No. women	40	35	32
RR (95% CI)	1.0	1.9 (1.2-3.1)	3.0 (1.7-5.2)
ERR/Gy (95% CI)		0.9 (0.3-2.3)	

Adapted from Hall et al., 1996b

who received I-131 therapy, 10,000 patients treated with thyroidectomy, and 2,500 who received anti-thyroid drugs. The patients in both studies were adults when treated with I-131. In Sweden, over 40% of the patients had hyperthyroidism due to toxic nodular goiter compared with only 8% in the U.S. study. Since toxic nodular goiter requires larger amounts of iodine for successful treatment, the total mean administered activity was higher in Sweden (13.7 mCi) than in the U.S. (10.4 mCi).

The SIR was 1.3 (95% CI=0.8-2.0) for all Swedish patients, 0.81 (95% CI = 0.30-1.8) for Graves' disease patients, and 1.7 (95% CI = 0.84-3.2) for toxic nodular goiter patients. Risk did not vary with time since exposure (Holm et al., 1991). The standardized mortality ratio (SMR) was 1.95 (95% CI = 1.01-3.4), but most of the increased mortality occurred during the first year after treatment (Hall et al., 1992). More than one year after treatment, a significantly increased risk of thyroid cancer mortality was observed among the U.S. I-131 treated patients compared with the number of expected deaths (Ron et al., 1998). More than five years after treatment, risk was increased for patients with Graves' disease and toxic nodular goiter but the risk was statistically significant only among toxic nodular goiter patients. The risk appeared to increase with increasing I-131 administered activity, but the exposure-response trend was not significant more than ten years after treatment. The study suggested that while there might be an association between thyroid cancer mortality and I-131 therapy, the attributable risk would be very small. Franklyn et al., (1998) evaluated mortality after I-131 treatment in a cohort of 7,209 hyperthyroid patients in England. They reported no excess cancer mortality, but did not present results for individual cancer sites.

The extremely limited data available on childhood I-131 medical exposure are insufficient to convincingly show a difference between the carcinogenic effectiveness of I-131 and external radiation. In addition to the 2,000 Swedish patients receiving diagnostic I-131 before age 20 (almost all of whom were between the ages of 15 and 19), about 3,500 U.S. patients who had I-131 exams before age 20 were studied by the FDA (Hamilton et al., 1989; Chiacchierini, 1990). The mean and median doses were estimated to be less than 0.5 Gy, but the authors state that the doses were probably somewhat higher because exams with incomplete data were not included in the dosimetry calculations. Four thyroid cancers were diagnosed among the cohort members. The relative risk was 2.96 (95% CI = 0.3-70) when the exposed patients were compared to the small internal non-exposed group, and slightly greater than 1 when U.S. population rates were used as the comparison.

Environmental Exposure to I-131

Marshall Islands

In 1954, people living in the Marshall Islands were accidentally exposed to heavy radioactive fallout when the wind changed unexpectedly during a nuclear weapons test in the Pacific Ocean (Conard, 1984; Hamilton et al., 1987; Robbins and Adams, 1989). The Marshall Islanders have exhibited an excess of thyroid carcinoma at thyroid doses estimated at between 7 and 14 Gy for young children and approximately 20 Gy for infants. Hamilton et al. (1987) reported that the prevalence of palpable thyroid nodules decreased with increasing distance from the test site. Takahashi et al. (1997) also found that nodule prevalence decreased with increasing distance, but they did not observe a relationship between present levels of Cesium-137 and distance. Since 80-90% of the thyroid dose absorbed by the thyroid was from the short-lived radioisotopes and gamma radiation, studies of the Marshall Islanders do not provide much information on the specific risks of I-131 (Robbins and Adams, 1989).

Nevada Test Site

Among almost 2,500 examined school children living in Nevada, Utah, or Arizona during the years of the nuclear weapons testing at the Nevada Test Site, 8 thyroid cancers were diagnosed compared with 5.4 expected (Kerber et al., 1993). The mean thyroid dose was 0.17 Gy. The excess risk was large (ERR $_{1Gy}$ = 7.9), but was not statistically significant. When benign and malignant tumors were combined, the risk reached statistical significance (ERR $_{1Gy}$ = 7.0; P = 0.02).

In response to a Congressional mandate, the National Cancer Institute (NCI) assessed exposure to I-131 fallout from atmospheric nuclear bomb tests conducted in the Nevada desert in the 1950s and 1960s (NCI, 1997). I-131 is the radionuclide of main concern because it is the principal radionuclide in fallout and it is ingested through consuming contaminated milk. Approximately 150 million Ci of I-131 were released into the atmosphere resulting in radioiodine deposition throughout the U.S. I-131 thyroid doses were estimated for each county in the continental United States by age group, gender, and level of milk consumption.

The average thyroid dose to the approximately 160 million people living in the U.S. during the time of testing was 20 mGy. The estimated dose varied

substantially depending on geographic location, age at the time of exposure, and quantity, source, and type of milk intake. Doses were highest east of the test site in Nevada and Utah and in some counties in Idaho, Montana, New Mexico, Colorado and Missouri and were lowest on the west coast, on the border with Mexico, and in parts of Texas and Florida. Due to geographic differences doses ranged from 0.01 to 160 mGy. The average dose to young children was approximately 10 times higher than the estimated adult dose because the thyroid gland of small children concentrates more iodine and because children drink substantially more milk than adults. While the uncertainties associated with estimating the average thyroid dose to the U.S. population is about a factor of 2, the uncertainty in dose estimates for individuals is about a factor of 3.

Because direct data on health effects of I-131 exposure are limited, the number of thyroid cancers expected to develop as a result of the I-131 exposure from fallout could not be estimated with any certainty. Scientists at the NCI used two methods, both of them requiring extrapolation from what is known about external radiation, to assess the risk of thyroid cancer. Land (1997) estimated the number of lifetime excess thyroid cancers based on a linear dose-response, age-specific risk co-efficients as reported by Ron et al., (1995), no gender differences in risk, a constant ERR over lifetime, and lifetime thyroid cancer rates of 0.25% and 0.64% for men and women, respectively. Depending on the assumed value for the relative biological effectiveness (RBE) of I-131 relative to external radiation, the predicted lifetime excess thyroid cancers ranged from 7,500 to 75,000 with a 95% uncertainty interval of 1,700-32,000 and 17,000-324,000, respectively. Based on an RBE of 0.66, the estimate was 49,000 (95% uncertainty interval = 11,300-212,000). Using a probabilistic distribution of RBE values, Hoffman (1997) predicted 46,000 (95% uncertainty interval = 8,000-208,000) lifetime excess thyroid cancer cases. In a review of the NCI estimates of I-131 thyroid doses from fallout and of their public health implications, the National Research Council/Institute of Medicine (1998) of the National Academy of Sciences concluded that the number of thyroid cancers attributable to the fallout is likely to be on the low end of the NCI predictions of 11,300 to 212,000.

Gilbert et al. (1998) related age-calendar year-sex and county-specific U.S. thyroid cancer mortality and incidence rates to I-131 dose estimates, taking geographic location, age at exposure, and birth cohort into account. Altogether 4,602 thyroid cancer deaths in 3,053 counties and 12,657 incident thyroid cancers in 194 counties covered by eight SEER cancer registries were included in the analyses. Neither cumulative dose nor dose

received between one and fifteen years of age were associated with thyroid cancer incidence or mortality. An association was suggested for dose received before age one (ERR $_{1Gy}$ = 10.6; 95% CI=1.1-29 and ERR $_{1Gy}$ = 2.4; 95% CI=0.5-5.6 for mortality and incidence data, respectively). Based on mortality data alone, an elevated risk was observed for the 1950-1959 birth cohort (ERR $_{1Gy}$ = 12.0; 95% CI = 2.8-31) (Figure 2). The absence of an increased risk from dose received after age one is not consistent with studies of external exposure, but may be due to inherent weaknesses in ecologic studies, as well as the large uncertainties associated with individual county dose estimates.

Hanford Atmospheric Releases

Between 1944 and 1957, the Hanford Nuclear Site in Washington State released between 500,000 and 700,000 Ci of I-131 into the atmosphere during the fuel processing step. In January 1999, the results of the Congressionally mandated Hanford Thyroid Disease Study (HTDS) were released to the public (Davis et al., 1999). In total, 5,199 people born between 1940 and 1946 in seven counties in eastern Washington State were identified for study. Ninety-four percent were located, 4,350 (84%) were alive, and 3,441 (66%) agreed to participate in the study. Study participants provided information on place of residence, milk and other relevant food consumption, occupational history, selected lifestyle factors, and medical history. Thyroid doses were estimated for the 3,193 study participants who had lived near Hanford during the period of atmospheric releases based on individual characteristics, e.g. level and type of milk consumption, and dosimetry information from the Hanford Environmental Dose Reconstruction (HEDR) project. The other 248 participants had moved from the Hanford area and were considered to have received no exposure. The mean and median doses were 186 mGy and 100 mGy, respectively. The distribution of dose was skewed (range 0-2,842 mGy) with a high percent of participants having low doses and only a small percent having high doses. Each participant was clinically evaluated by two study physicians. The examination included ultrasound, thyroid palpation, and blood tests. Eleven categories of thyroid disease, ultrasound-detected abnormalities, and hyperparathyroidism were evaluated in terms of estimated I-131 radiation dose to the thyroid.

A total of 19 participants were diagnosed with thyroid cancer and 249 with benign thyroid nodules (Table 3). No evidence of a dose-response relation was found for malignant or benign nodules or any of the other outcomes

Table 3- *Frequency of thyroid nodules by dose received from the Hanford Nuclear Site atmospheric releases of I-131.*

Thyroid Nodules	Thyroid dose (mGy)						
	0	0-	10-	50-	100-	200-	400+
Malignant							
Persons examined	5	1	6	1	3	2	1
%	2.0	0.29	1.1	0.17	0.45	0.32	0.26
Benign							
Persons examined	14	26	44	34	64	45	22
%	5.6	7.6	7.7	5.7	9.6	7.1	5.7

studied. The investigators reported that the study had 95% power to detect a 5% per Gy increase in benign thyroid nodules and 96% power to detect a 2.5% per Gy increase in carcinoma. To date, criticism of the study has centered around the following points: 1) needed modifications to the HEDR dose model might impact on the individual doses calculated for the study participants, 2) individual thyroid doses have considerably more uncertainty than the HEDR calculated representative doses and this additional uncertainty decreases the likelihood of detecting an effect, 3) the power calculations did not consider all sources of uncertainty and, therefore, are overestimated, and 4) while exposure from the Nevada tests was taken into account in the analyses, the level of uncertainty for these doses is large enough to dilute the HTDS results. The final report is yet to be published and further peer review is needed. Nevertheless, these results provide no evidence that I-131 doses on the order of 100 mGy increase the risk of developing thyroid neoplasia.

Chernobyl

Four years after the Chernobyl nuclear power plant accident in April 1986, childhood thyroid cancer began to appear in contaminated areas, particularly southern Belarus, northern Ukraine, and adjacent areas in western Russia (Kazakov et al., 1992; Baverstock et al., 1992; Likhtaryov et al., 1995; Stsjazhka et al., 1995; Williams, 1994). About 40 million Ci of I-131 were released at the time of the accident. It has been estimated that I-131 contributed as much as 70% of the internal thyroid dose to the population living in the contaminated areas (Zvonova and Balonov, 1993).

The short-lived iodines primarily contributed to exposure very close to the Chernobyl plant. The short latency (<5 years) and the thyroid screening conducted in the contaminated areas led to questions about the causal role of radiation (Beral and Reeves, 1992; Ron et al., 1992; Shigematsu and Thiessen, 1992). However, more than ten years after the accident, the association between radiation and thyroid cancer seems clear, although a reliable risk estimate has not yet been determined (Karaoglou et al., 1996; Astakhova et al., 1998; Sobolev et al., 1997; Jacob et al., 1998).

In Belarus, 1,342 adult and 7 childhood thyroid cancers were diagnosed in the 10-year period before the Chernobyl accident, whereas 4,006 adult and 508 childhood thyroid cancers were reported after the accident (Demidchik et al., 1996). Birth-cohort analyses have demonstrated an enormous increase in thyroid cancer incidence after the accident among young Ukrainian children exposed to fallout from Chernobyl (Sobolev et al., 1996) (Table 4). In Russia, an increase in thyroid cancer also was observed, but it occurred somewhat later than in either Belarus or Ukraine (Tsyb et al., 1996). Two recent studies have linked estimated thyroid dose to thyroid cancer incidence. In a case-control study with 107 cases and 107 controls, conducted in Belarus, a statistically significant dose-response was demonstrated (Astakhova et al., 1998) (Table 5). In an ecological study with detailed dose-reconstruction data for the contaminated areas of Ukraine, Belarus and Russia, a linear dose-response relation was found and the excess absolute risk was consistent with risks reported following external exposure (Jacob et al., 1998).

The extremely early and high risks observed among children exposed to Chernobyl fallout raises the question of whether there might be an interaction between radiation and other factors. Iodine deficiency has been suggested as one possible factor (Gembicki et al., 1997). Between 1986 and 1990, hundreds of thousands of civilian workers, military servicemen, scientists and medical staff from the former Soviet Union were involved in entombing the damaged reactor and cleaning up the contaminated environment. About 225,000 workers, mostly male, were employed in the 30-km zone during the first year after the accident. The radiation dose limit for workers was originally set at 0.25 Gy for total service in Chernobyl, but in 1987 it was reduced to 0.1 Gy, and in 1988 to 0.05 Gy. In addition to external radiation, workers who were on site during the first few weeks after the accident also were exposed to radioiodines. Estimated individual external doses have a large degree of uncertainty, and doses from internally-deposited radioiodines are hardly known.

Table 4- *Annual age-specific incidence of thyroid cancer from 1986 to 1994 among people exposed to radiation from Chernobyl by year of birth[a].*

Age	Year of birth								
	1968-1969	1970-1971	1972-1973	1974-1975	1976-1977	1978-1979	1980-1981	1982-1983	1984-1985
0-									-
3-								-	0.22[b]
5-							0.34	-	1.9
7-						0.35	0.69	2.6	7.5
9-					1.4	2.1	3.8	3.6	6.4
11-				1.0	1.7	4.1	9.2	7.3	
13-			2.38	1.7	3.1	6.5	8.0		
15-		2.82	4.38	5.8	6.5	8.1			
17-	3.45	3.87	4.99	7.5	6.8				
19-	5.4	5.6	5.7	3.4					
21-	8.4	9.8	10.4						
23-	16.1	7.7							
25-	15.1								

[a] Adapted from Sobolev et al., 1996.
[b] Incidence per 10^4 persons.

Thyroid cancer incidence and mortality have been evaluated in a cohort of cleanup workers from Estonia (Rahu et al., 1997). No thyroid cancers were observed between 1986 and 1993 among 4,742 workers in the cohort, whereas 0.21 cases would have been expected based on age-sex and calendar-specific cancer incidence rates in Estonia. Among the 1,979 workers participating in a thyroid screening examination, including palpation and ultrasound, 2 thyroid cancers, 3 benign tumors, and 196 unspecified thyroid nodules were diagnosed (Inskip et al., 1997). Thyroid nodules were not associated with documented dose, type, time period, or duration of

Table 5-*Thyroid Cancer Risk Associated with I-131 Exposure from Chernobyl.*

	Estimated Thyroid Dose from I-131 (Gy)			
	<0.30	0.30-0.99	1.0+	RR
Cases	64	26	17	2.1
Population Controls	88	15	4	(1.7-5.8)
Cases	64	26	17	2.6
Medical Controls	84	19	4	(1.4-4.8)

Adapted from Astakhova et al.,1998

service in Chernobyl, or biological measures of dose. Film badges indicate that the mean external dose was 0.1 Gy, but based on fluorescence *in situ* hybridization (FISH), Littlefield et al., (1998) suggest that actual doses were lower. A different interpretation of these results is that FISH is not sufficiently sensitive to detect translocations at doses this low.

In the Russian Federation, 168,000 cleanup workers are being followed through annual medical check-ups (Ivanov et al., 1997a and 1997b). Through 1995, 47 thyroid cancers have been diagnosed; 43% were follicular, 33% papillary, and 14% other types of carcinoma. The estimated ERR/Gy was 5.31 (95% CI = 0.04-10.58) and the EAR/10 [4] PY Gy was 1.15 (95% CI = 0.08-2.22). Boice and Holm (1997) have criticized this study for not using internal comparisons and not accounting for increased medical surveillance among clean-up workers. They also noted that the workers have too short a latency period and that no elevated risk was observed among clean-up workers in Estonia. Ivanov et al., (1998b) contend that they adjusted for a screening effect, discounted the first four years after the accident, and that the cohort of Estonian cleanup workers was too small to detect an elevated risk of thyroid cancers. Additional follow-up will be needed to clarify these complicated issues.

Relative Biological Effectiveness of I-131

Early animal studies have suggested that the relative biological effectiveness of I-131 is between 2 and 20 times lower than for external radiation (Doniach, 1963; NCRP, 1985). Because the major concern at that time was the potential tumorigenic effects of I-131 therapy, most experimental studies

involved adult animals exposed to very high doses of radiation. At these doses cell-killing could confuse results. A more relevant experiment for today's interest in low doses and childhood exposure was conducted by Lee et al. (1982). In the largest experiment conducted to date, they studied 3,000 young female rats exposed to doses in the range of 1-10 Gy. The RBE for thyroid cancer was 1 and for thyroid adenomas it was 0.5. In a critical review of the literature, Royal (1999) noted that the Lee et al. (1982) study had a better experimental design than other animal studies, and that the diagnoses were confirmed by an independent blind review of the tumor tissue. Laird (1987) compared effects from I-131 with external radiation using data from epidemiological and animal studies and estimated an RBE of 0.7, however the 95% confidence interval was wide (95% CI = 0.14-3.15) and included 1. Because sufficient human data are not available to directly compare I-131 and external radiation, Brenner (1999) used microdosimetric and radiobiological information to assess the radiation quality of I-131 beta particles and 250 kVp x-rays. With three different endpoints (chromosomal aberrations, HPRT mutations and *in vitro* oncogenic transformation), the calculated RBE ranged from 0.54 to 0.62. Brenner reported that there was little evidence of a dose-rate effect at low doses and concluded that the overall effectiveness of I-131 was about 0.6.

Summary and Discussion

The human data on childhood exposure to external radiation clearly demonstrate that it is an important cause of thyroid cancer. They also indicate that the dose-response is linear, that risk increases with decreasing age at exposure and that an increased risk continues for at least 40 years. The data on I-131 are too limited to adequately quantify the risk of thyroid cancer or to describe risk patterns. However, recent epidemiological studies conducted in areas contaminated by the Chernobyl accident indicate a dose-response relation between radioiondines, primarily I-131 and thyroid cancer incidence. Risk also appears to be higher among persons exposed as very young children. Data on adult exposure suggest that neither I-131 nor external radiation are associated with elevated risks of thyroid cancer.

Epidemiological investigations of the association between thyroid cancer and radiation have several potential methodologic difficulties and limitations. Because of the rarity of the disease, the number of cancers in any one study is often too small to have adequate statistical power and precision. Detection bias also can be a problem because radiation-exposed populations frequently are screened or receive more thorough thyroid examinations than

non-exposed populations. In addition, dosimetry for radionuclides is generally more complicated than for external radiation. In medical exposures, there is little correlation between the amount of I-131 administered activity and thyroid dose estimates (Becker and Hurley, 1996). Assessment of environmental exposure is substantially more difficult because it requires retrospective dose reconstruction which, at times, relies on few actual physical measurements, self-reported milk and vegetable consumption, detailed residential history, assumed feeding patterns of milk producing animals, and methods of storage, handling, and transportation of milk. When the large uncertainties associated with retrospective thyroid dose estimates from environmental I-131 exposure are incorporated in the analysis of epidemiologic studies, the resulting risk estimates have extremely wide confidence intervals and therefore, need to be interpreted cautiously.

Nevertheless, it is expected that additional research conducted in Chernobyl will help reduce the uncertainties in dose estimates, clarify the role of other, potential confounding, factors and improve our understanding of the tumorigenic effects of internal radiation. Possibly more can be learned from pooling the medical studies of I-131 or from expanding existing cohorts to increase the number of patients exposed to I-131 in childhood. Meantime, a review of the accumulated knowledge from epidemiological, experimental, and theoretical research suggests that 0.6 is a reasonable estimate of the RBE for I-131.

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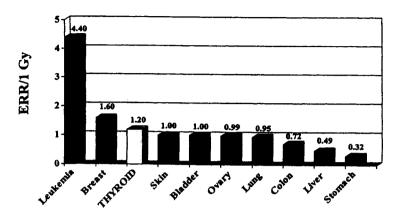# Cancer Incidence Risks:
A-bomb Survivors, 1958-87

Figure 1. Ranking of major cancer incidence sites by excess relative risk in Life Span Study, 1958-1987

ESTIMATED EXCESS RELATIVE RISK PER Gy (WITH 95% CI) BY AGE AT EXPOSURE
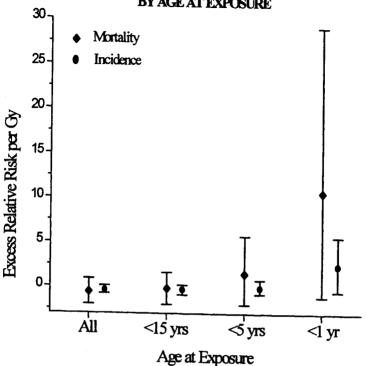
Figure 2 - Thyroid cancer risk from I-131 exposure during atmospheric nuclear testing at the Nevada Test Site, 1952-1961.